Thrombotic Microangiopathy: Multi-Institutional Review of Pediatric Patients Who Underwent HSCT

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Abstract

Thrombotic microangiopathy (TMA) is a rare but serious complication of hematopoietic stem cell transplantation (HSCT). The purpose of our study is to estimate the incidence and risk factors of TMA in 93 out of a total of 12369 children (0.8%) receiving HSCT. HHV6 infection was an independent risk factor associated with increased mortality in patients with TMA (Hazard Ratio: 2.86 [1.01, 8.39], p=0.05), and our study conducts a review of the literature with the association of HHV-6 and complement activation. Studies exploring the pathophysiology of TMA and its relationship to HSCT are needed to optimize the outcome of pediatric patients.

Introduction

Transplant-associated thrombotic microangiopathy (TA-TMA) is a rare but serious complication of hematopoietic stem cell transplantation (HSCT). As a part of the family of thrombotic endothelium disorders, the disease causes microangiopathic hemolytic anemia leading to microvascular thrombosis and fibrin deposition in the microvessels. Due to a lack of clear diagnostic criteria, it is difficult to determine incidence and mortality for the disease, but values are estimated to range from 3% to 39% for incidence and exceed 50% for mortality ([1,2,3]).

Currently, research shows that TMA is induced by endothelial cell injury which could be the result of either infection, graft-versus-host disease (GVHD), chemotherapy or radiation.

Literature demonstrates increased incidence status post allogeneic HCST when compared to its autologous counterpart ([...][4,5]). While a few case studies of pediatric patients note that TA-TMA was preceded by a HHV6 infection, there is an ultimate lack of data regarding HHV6 association with TA-TMA ([5]). The purpose of our study is to estimate the incidence of TA-TMA in children receiving HSCT and reveal other potential risk factors and its impact on healthcare outcomes in this population.

Methods

We used the Pediatric Health Information System (PHIS), an electronic database of children's hospitals in the US. The study was deemed exempt by the local Institutional Review Board. De-identified patients under the age of 21 who underwent HSCT at one of the 42 PHIS hospitals from 2000-2012 were analyzed using data abstracted with ICD-9 codes. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC) or the base R statistical package (R Foundation for Statistical Computing, Vienna, Austria). All calculated P values were 2-sided, and $P < .05$ were considered statistically significant.

Results

From 2000 to 2012, a total of 12369 unique pediatric patients who received HSCT were identified. Among these 93 (0.8%) children were identified to have the diagnosis of TMA. Overall, there was an increasing trend of TMA diagnosis seen in our cohort over the years, with the highest percent occurrence in 2012 (p = 0.0125).

In Table 1, we identified 12 cases of TMA (12.9%) in patients who received an autologous HSCT, 78 cases (83.9%) in patients who received an allogeneic transplant, and 3 cases (3.2%) who were unspecified. Furthermore, 25 cases of TMA (32.1%) were from a bone marrow transplant, 41 cases (52.6%) were after a peripheral blood transplant, and 12 cases (15.4%) occurred after a cord blood transplant.

TMA was significantly associated with allogeneic HSCT (p=<0.001), PBSCT (p=0.045), CMV (p=<0.001), HHV6 (p=<0.001), fungal infection (p=<0.001), GVHD (p=<0.001) and VOD (p=0.01). Additionally, TMA was significantly associated with hypertension (p=<0.001), and renal failure (p=<0.001) (Table 1). Multivariate logistic regression analysis of mortality using age, gender, HSCT type, CMV, HHV6, fungal infection and plasmapheresis showed only HHV6 was an independent risk factor associated with increased mortality in patients with TMA (Hazard Ratio: 2.86 [1.01, 8.39], p=0.05)

The mortality was significantly higher in patients with TMA compared to those without (30.1% vs. 12.2%, p=<0.001, Table 1). Additionally, median time (days) to mortality following HSCT was shorter in patients with TMA than those without (754 [365, 1614] vs. 1439 [552, 2847], p=<0.0001).

Discussion:

Thrombotic microangiopathy is a severe complication seen following HSCT in children, thought to be associated or preceded by graft-versus-host disease (GVHD). We are currently working in the paradigm of a three-hit hypothesis, where patients with underlying genetic factors (Hit 1) that undergo conditioning regimens such as chemotherapy and/or radiation (Hit 2) and experience other potential sources of endothelial injury such as infection, medication or GVHD symptoms (Hit 3) are more likely to manifest the disease ([6]).

As demonstrated by previous literature, our data show higher incidence of transplant-associated thrombotic microangiopathy (TA-TMA) after allogeneic HSCT when compared to its autologous counterpart ([7,8]). Prior literature has documented increased risk of both acute and chronic GVHD associated with peripheral blood HSCT ([9,10]). Additionally, GVHD association with TA-TMA is both well-documented and in agreement with our data ([11,12]). We also discovered, in concordance with the literature, that GVHD had a higher association with late TMA, defined as TMA that presents 120 days after transplant, compared to early TMA (p = 0.03) ([13]).

In chronic GVHD, the endothelium can be damaged as a result of cytotoxic T-cell induced injury ([14]). Other studies have also shown that many of the immunosuppressive agents used to treat GVHD, such as calcineurin inhibitors can cause damage to the endothelium ([15,16]). Treatments given following transplant such as radiation and chemotherapy are also known to be associated with development of TA-TMA ([17–19]).

Our data shows a significant correlation between CMV, HHV6, and fungal infections post-transplant and risk of TA-TMA ([20]). Interestingly, we also found that HHV6 infection increases both risk and mortality in addition to risk of TA-TMA. HHV6 is known to directly infect endothelial cells and inhibit angiogenesis ([21]). Several studies have noted elevated levels of neutrophil extracellular traps (NETs) in patients with TA-TMA ([22]). Mechanistically, it is believed that IL-8 is released by the damaged endothelial tissue, recruiting neutrophils that will undergo netosis and form NETs. These NETs, known up-regulators of complement, then induce complement activation on self-cells, leading to TA-TMA. While normally NETs may be cleared, in patients with chronic GVHD undergoing treatment, the endothelium is constantly being attacked ([23]). In patients additionally infected with HHV6, angiogenesis is inhibited, affecting the body's ability to repair this damage **([24]).**

HHV6 infection may simply play a role in TA-TMA via GVHD as many studies identify HHV6 species B as a risk factor for acute GVHD after HSCT ([24]). It is also of specific interest that the cellular receptor for HHV6B in humans is CD46 or Membrane Cofactor Protein (MCP), a regulator of complement attack

on self-cells. In T-cells, it is documented that HHV6B infection leads to down-regulation of MCP ([25]). Although there is no data on MCP expression on endothelial cells after HHV6B infection, it seems possible that the same finding could hold true for both cell types, see proposed mechanism in Figure 1 ([26]). If MCP expression is reduced, endothelial cells become more prone to damage via complement attack. While more data is needed to corroborate this claim, HHV6 induced downregulation of MCP along with promotion of complement signaling via NETs would serve to further expose endothelial cells to damage complement attack and therefore promote development of TMA ([27]).

Limitations of the study relate to the age of the data collected between 2000 and 2012, however we believe that our discoveries remain relevant. PHIS is an administrative database, therefore the patients studied here were identified utilizing ICD-9 codes, which may not fully reflect all complications.

Conclusions

Ours is a large cohort of TMA following HSCT in children. The prevalence of TMA in our study is 0.8% with an increasing trend in recent years. The mortality in our pediatric TMA cohort is 30% which is in contrast to the higher mortality reported in previously published small case series. HHV6 emerged as not only a risk factor for TMA but also associated with increased mortality in these patients. Studies exploring the pathophysiology of TMA and its relationship to other complications of HSCT and to prove the effect of HHV6 on complement on a molecular level are needed to optimize the outcome.

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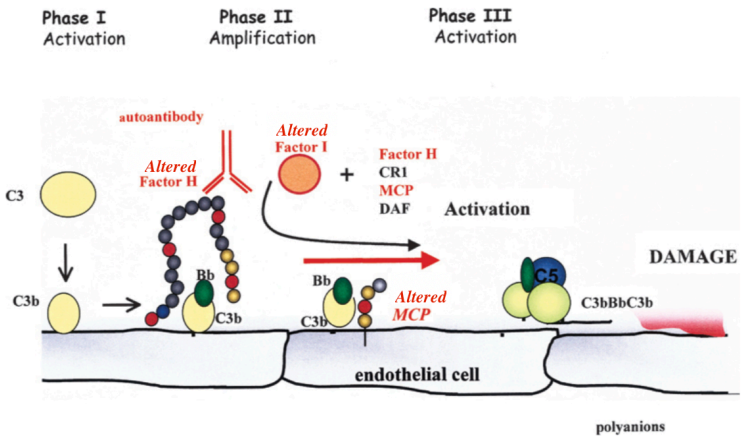

Figure 2: Proposed MCP Expression on Endothelial Cells After HHV6 Infection